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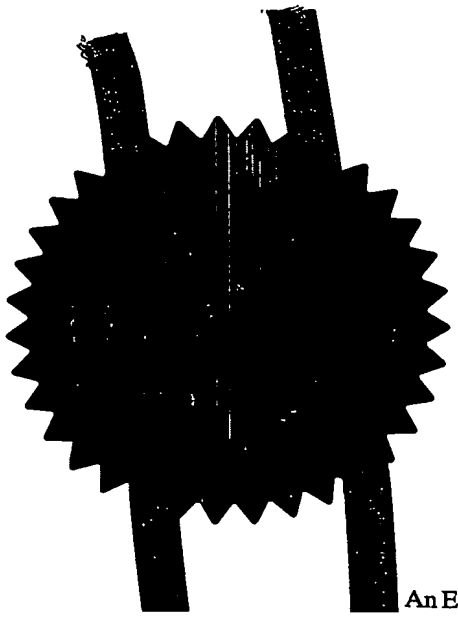

Signed R. Mahoney

Dated 20 October 2003

GB 0221986.3

By virtue of a direction given under Section 30 of the Patents Act 1977, the application is proceeding in the name of

BIOPROGRESS TECHNOLOGY INTERNATIONAL INC,
9055 Huntcliff Trace,
Atlanta,
Georgia 30350,
United States of America

Incorporated in USA - Nevada,

[ADP No. 08219669001]

Patents Form 1/77

Patents Act 1977
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Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

1. Your reference P13

2. Patent application number *(The Patent Office will fill in this part)* 0221986.3 30/6/03

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

BIOPROGRESS TECHNOLOGY LIMITED
HOSTMOOR AVENUE
MARCH TRADING ESTATE
MARCH
CAMBRIDGESHIRE PE15 0AX

Patents ADP number *(if you know it)* 07743830002

If the applicant is a corporate body, give the country/state of its incorporation

4. Title of the invention

FILMS WITH IMPROVED BARRIER PROPERTIES

5. Name of your agent *(if you have one)*

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

BIOPROGRESS TECHNOLOGY LIMITED
HOSTMOOR AVENUE
MARCH TRADING ESTATE
MARCH
CAMBRIDGESHIRE PE15 0AX

Patents ADP number *(if you know it)*

	Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*
6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number			

	Number of earlier application	Date of filing *(day / month / year)*
7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application		

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.
See note (d))

YES

Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	
Description	7
Claim(s)	1
Abstract	0
Drawing(s)	3 + 3

10. If you are also filing any of the following, state how many against each item.

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Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application.

Signature [signature] Date 20/9/02

12. Name and daytime telephone number of person to contact in the United Kingdom SIMON JONES 01354 602192

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Notes

a) *If you need help to fill in this form or you have any questions, please contact the Patent Office on 08459 500505.*

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Films with Improved Barrier Properties

Field of the Invention

This invention relates to modified polymeric materials and more particularly films of the modified cellulose material hydroxy propyl methyl cellulose (HPMC), and uses of such film.

Background of invention

HPMC is a synthetic plastics material, which is a chemically modified form of the naturally occurring polymer, cellulose. Films, (or sheets or membranes) of HPMC are available commercially and have various uses, including proposals for use as wall materials for delivery capsules i.e. capsules designed to retain and protect their contents until an intended site of delivery or conditions of delivery are encountered, at which the contents of the capsule are released. HPMC is suitable for ingestion by humans, so delivery capsules with HPMC walls find the potential use as ingestible capsules, e.g. for the delivery of accurately metered doses of pharmaceutical preparations and dietary supplements, as a possible replacement for gelatin based capsules. See for example, WO 97/35537, WO00/27367 and WO01/03676. HPMC can be used to encapsulate substances, such as pharmaceuticals or food supplements like fish oils. It is known that certain pharmaceuticals and food supplements can be prone to attack by extended exposure to e.g. air, and it is preferable to encapsulate many unrefined vegetable oils and fish oils to prevent them from going rancid. However, even when these substances are encapsulated, .e.g. within HPMC film, they can still be prone to oxidation, e.g. by the film wall of the capsule allowing oxygen present in the air outside the capsule, to pass through into the inside of the capsule some coming into contact with the capsule's contents, and reacting with the contents in some way to spoil the contents.

HPMC has poor resistance to oxygen transmission relative to other hydrocolloid film forming materials, such as gelatin, alginates, pectins and some other natural polymers. To improve oxygen barrier properties of the HPMC film, the film can be coated with hydrocolloids, for example, alginates. However, the coating of these films does give rise to certain disadvantages, such as creating films with multiple layers of materials each layer perhaps possessing different physical/chemical properties and thus creating increased processing complexities and problems arising therefrom, resulting in an increase in time and costs for film production.

Acetins are already known as film additives for certain film materials, but untreated films and films treated with acetins and /or other additives can show very poor resistance to oxygen penetration. However, it has now been surprisingly discovered

that by incorporating various carboxylic acids, especially alpha hydroxy acids and beta hydroxy acids within HPMC film, it is possible to reduce the oxidation of vegetable and fish oils encapsulated in capsules made from this film.

Summary of the invention

In one aspect of the present invention provides hydroxypropyl methyl cellulose film, comprising hydroxypropyl methyl cellulose and an additive comprising an organic acid, or derivative or salt of such an acid.

Suitable organic acids are carboxylic acids, such as mono, di, tri, or tetra or other polyvalent carboxylic acids.

Carboxylic acids according to the present invention include the following:

C1-C6 saturated or unsaturated, straight or branched chain carboxylic acids, with 1,2,3 or 4 carboxyl groups
C1-C6 hydroxy acids with any combination of 1,2,3,4 hydroxyl/carboxyl groups, including alpha hydroxy acids (AHA's) and beta hydroxy acids (BHA's)
Cyclised acids and cyclised hydroxy acids

Specific examples of acids according to the present invention include the following:

carboxylic acids

Adipic acid
Fumaric acid
Maleic acid
Proprionic acid
Salicylic acid
Ethanoic acid
Propanoic acid
Butanoic acid
Pentanoic acid
Hexanoic acid

hydroxy acids

Alpha hydroxy butyric acid
Mandelic acid
Tartaric acid
Lactic acid
Citric acid
Malic acid
Glycolic acid
Hydroxy citric acid

cyclised acids and cyclised hydroxy acids

Gamma butyrolactone
Gamma valerolactone
Beta propriolactone

HPMC films can be treated with alpha and beta hydroxy acids and also other carboxylic acids derived from fruit acids to produce clear films which can then be used to produce capsules which can significantly reduce oxidation of certain substances encapsulated within same as compared with capsules made form HPMC treated with compounds such as glycerine, propylene glycol, poly ethylene glycol and acetins. This significant improvement in the reduction of oxidation is thought to be attributable to the acid additive incorporated within the film perhaps hindering oxygen transmission through the film.

These films can be improved or modified further to suit the application by coating these films with aqueous solutions containing the acids according to the present invention.

In a first aspect of the invention, the acids are incorporated within the film by simply admixing the acids within a film forming resin which is then formed into a film.

In a second aspect of the invention, aqueous solutions of the acids are applied to the surface of a preformed film.

In another aspect of the present invention, aqueous solutions of acids are applied to the surface of (a) film(s) to bond two HPMC films together with favourable barrier properties.

Film Manufacture

HPMC is dissolved in water with an acid or acids according to the present invention e.g. citric acid, to make a solution of which the total solids being between 10-20% w/w. (During this procedure, optional ingredients such as dyestuffs, sweeteners and manufacturing aids can be added.) The resultant viscous solution is then de-aerated and extruded at a set thickness onto a moving (endless) steel belt of which, during the length of its travel is heated to 80-100 degrees centigrade. During this heating process, water is evaporated from the film, leaving a dry film of thickness between 20-150 microns. This film is then removed from the belt and is further processed for use, e.g. slitting to a final roll width, laminating the single ply film to yield a double ply film, or coating with an external coat to give a specific desired property. Alternatively, for smaller quantities of film, a viscous solution can be poured onto a flat sheet of glass, and allowed to settle to form a flat bed of viscous liquid which lies on top of the glass. This can then be introduced into an oven at the desired temperature, where it can be left to dry , to form a desired sheet of film.

Preparation of capsules

A film solution consisting of HPMC and acid according to the present invention (total solids 10%) is cast onto glass plates to a set thickness. The cast film is then placed in a warm oven (50-80 degrees centigrade) to form a rigid film , which is then removed from the glass plate and left to equilibrate at room temperature. The resulting film produced is then placed on a vacuum forming bed and thermoformed into cavities or half capsules. Each cavity is filled (overfull) with fish or vegetable oil and lidded with an identical sheet of HPMC film. A heated tool is then used to seal the films together and to cut the resulting capsules free of excess unused film surrounding the cavities. The capsules formed are removed from the bed and packed and placed in storage.

Stability testing

The stability of fish and vegetable oils were evaluated in the capsules made in accordance with the present invention. The stability of the oil in the capsules was evaluated by analysing the peroxide value (P.V.) over time.

Using a standard pharmaceutical test, samples were prepared and stored in HDPE bottles at 30 degrees centigrade, 60% relative humidity. Periodically, the samples were removed and analysed according to method described in the European Phamacopea: Peroxide Values Ph.Eur. method 2.5.5.

The results were plotted graphically to show comparative changes in P.V. over time.

Control capsules were made from HPMC film incorporating acetins (mono and diacetin).

The results can be interpreted thus: The higher rate of peroxide generated in the oil, the less stable is the end product.
Therefore , the best performing films show lower peroxide values.

Formulations:

Graph 1 and 2	%w/w
HPMC (Methocel E50 ex Dow)	77
Diacetin	23
HPMC	77
Lactic acid	23
HPMC	77
Lactic acid	11
Citric acid	12
HPMC	77
Citric acid (anhydrous)	20
Glycerin	3
HPMC	77
Citric acid (anhydrous)	23

Figure 3	
HPMC	77
Monoacetin	23
HPMC	77
Lactic acid	23
HPMC	77
Malic acid	23
HPMC	77
Citric acid	23

Interpretation

Graph 1 – capsules containing evening primrose oil (EPO)

Demonstrates the superior performance of HPMC incorporating citric acid or citric acid/glycerin combinations within the capsule film, by revealing generally lower and slowly rising peroxide values over a 5 month period. A 1:1 lactic/citric combination in the film still demonstrates very good performance and films treated solely with lactic acid still show a marked improvement over the performance of film treated with diacetin (control), a known film additive.

Graph 2 – capsules containing fish oil (Lipromega TG60)

General trends shown in graph 1 are also demonstrated here. A vast improvement in maintaining low P.V. is shown. demonstrated by the stark stablizing effect of citric acid.

Graph 3 – capsules containing fish oil (Lipromega TG60).

In this test, capsules were exposed directly to the atmosphere (without any packaging around the capsules). HPMC films containing citric, malic and lactic acid (especially citric and malic acids) demonstrated superior performance with respect to peroxide values, over HPMC films containing monoacetin.

Claims

1. A hydroxypropyl methyl cellulose film, comprising hydroxypropyl methyl cellulose and a barrier composition comprising an organic acid or a salt of an organic acid.

2. A film according to claim 1, wherein the organic acid is a carboxylic acid.

3. A film according to claim 1 wherein, the organic acid comprises one or more of maleic acid, fumaric acid, adipic acid, citric acid, lactic acid.

4. A film according to claim 1 wherein the organic acid comprises citric acid.

5. A film according to claim 1 wherein the organic acid comprises malic acid.

6. A film according to claims 1-5 wherein the organic acid is present in the amount in the range 5 to 40% by weight of the total weight of the film.

7. A film according to claims 1-6 comprising about 23% by weight of organic acid and 77% by weight of HPMC.

8. A film according to any one of the preceding claims, wherein the film is foamed, expanded or gasified.

9. A film according to any one of the preceding claims wherein the film has a thickness of between 50 to 200 microns.

10. A film according to any one of the preceding claims, wherein the film is additionally treated with an aqueous acid composition made up of acids of any previous claim.

11. A 2-ply film made from the films according to any previous claim, wherein the 2 films are bonded to one another by an acid solution made up of acids in any previous claim.

12. A delivery capsule with an enclosing wall comprising a film in accordance with any one of the preceding claims.

13. A method of producing HPMC film suitable for forming into a capsule, comprising treating the HPMC film with acids in any preceding claim, before and/or during when the film is manipulated to form a capsule.

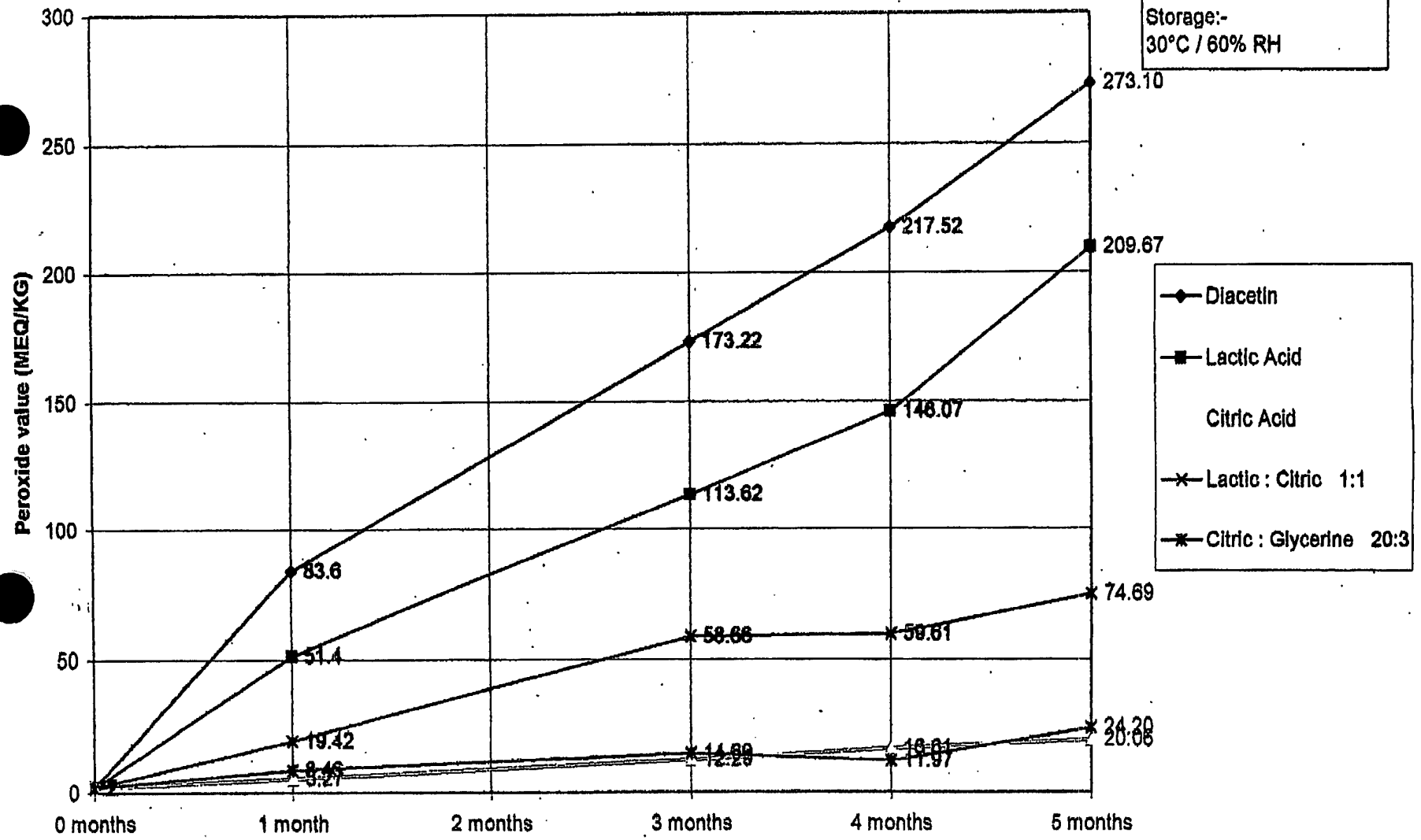
GRAPH 1

EPO # 1 / 02

HPMC **encapsulating EPO**

Packaging:-
HDPE bottles, ex PBH

Storage:-
30°C / 60% RH



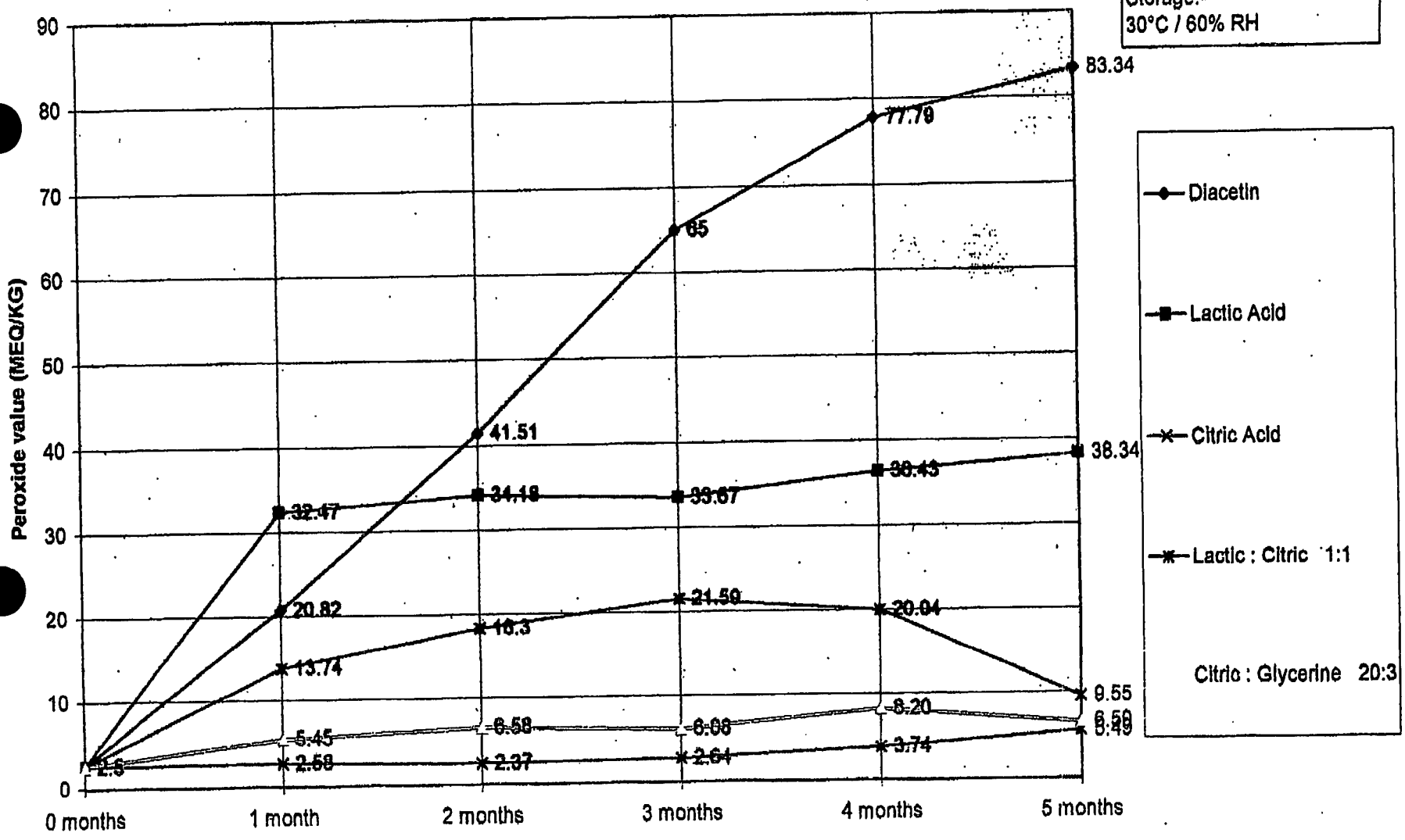
GRAPH 2

Lip.TG60 # 1 / 02

HPMC film **encapsulating Lipromega TG60**

Packaging:-
HDPE bottles, ex PBH

Storage:-
30°C / 60% RH



GRAPH 3

Lip.TG60 # 5 / 01

Uncoated HPMC film with Acids + control, encapsulating Lipromega